SMMGP CLINICAL UPDATE

April 2011

Alcohol use disorders. Diagnosis, assessment and management of harmful drinking and alcohol dependence. *National Institute for Health and Clinical Excellence. NICE Clinical Guideline 115. Feb 2011.*

This is the third piece of NICE guidance relating to alcohol and should be read in conjunction with their public health guidance (PH24) and the clinical guideline relating to the diagnosis and clinical management of alcohol-related physical complications (CG100).

NICE have a number of key priorities for implementation. They recommend that staff in *all* settings provided and funded by the NHS should be competent to identify harmful drinking and alcohol dependence. NICE recommend assessment using the AUDIT tool and anyone who scores more than 15 should be considered for a comprehensive assessment. It recommends the use of validated tools such as the Severity of Alcohol Dependence Questionnaire (SADQ), the Leeds Dependence Questionnaire (LDQ), the Alcohol Problems Questionnaire (APQ) and the Clinical Institute Withdrawal Assessment of Alcohol Scale, revised (CIWA-Ar). Other drug misuse should be assessed, as should physical, psychological and cognitive function (using, for example, the Mini-Mental State Examination).

They recommend that harmful drinkers and those with mild alcohol dependence should be offered a 'psychological intervention' but this can be broadly interpreted. NICE recommend that for people with mild to moderate dependence we should offer an outpatient-based assisted withdrawal programme in which contact between staff and the service user averages 2-4 meetings per week over the first week. Those who have complex needs, or have severe dependence, should be offered an intensive community programme following assisted withdrawal in which the service user attends for between 4 and 7 days per week over a 3-week period. Inpatient or residential withdrawal might be considered in those drinking over 30 units per day, scoring >30 on the SADQ, have other significant co-morbidities, or who may be vulnerable for other reasons e.g. homeless or older people.

The preferred medication for assisted withdrawal is a benzodiazepine such as chlordiazepoxide or diazepam. NICE suggest that after withdrawal we should consider offering acamprosate or oral naltrexone in combination with psychological interventions.

Alternatively, NICE have also suggested disulfiram in those who simply have a preference for it or who are not suitable for acamprosate or naltrexone.

SMMGP comment: The NICE guidance now offers a comprehensive set of guidelines for identifying, assessing and managing alcohol and its related problems. There is much here that will be pertinent to individual clinicians and for those seeking to develop new or existing services.

It is also worth delving into the associated documents – for instance, NICE provide sample chlordiazepoxide dosing regimens in a separate document. In this NICE state we should "*consider offering a benzodiazepine or carbamazepine*". They don't expand further on carbamazepine other than highlighting that it is unlicensed in these circumstances. Many clinicians now use carbamazepine where there is a risk of 'kindling' - the phenomenon where those that have had previous recent detoxifications are susceptible to more severe seizures in subsequent detoxifications.

We recommend the RCGP Certificate in the Management of Alcohol Problems in Primary Care if you want to develop your skills further in

both assessing people for alcohol problems and delivering brief interventions in general practice.

Alcohol and depression. *Boden JM, Fergusson DM. Addiction 2011; 106;906-914*

This systematic review looked at the literature on the association between alcohol use disorders (AUD) and major depression (MD). Specifically, it was looking at the evidence for a causal relationship between the two disorders.

The analysis showed that the presence of either disorder doubled the risks of the second disorder. The authors then went on to provide a narrative review of the evidence and suggested that the data shows there is a causal association and that the most plausible mechanism is one where AUD increases the risk of MD.

SMMGP comment: There is little doubt about the association between these two problems but the main challenge in the epidemiological studies has been to pull out all the confounding factors. Even after doing this, there seems to be a persistent relationship suggesting a causal relationship - so the question then moves on to the direction of causality. The authors present the case that it tends to be the alcohol causing depression and they go on to quote one study which suggests that up to 10% of the overall burden of major depression may be attributable to alcohol use disorders.

There are two commentaries on this article in Addiction and they both draw attention to the conclusion of the authors that AUD is more likely to be causal of MD than vice-versa. One commentary suggests this could also be something of a chicken and egg discussion and there is a certain amount of reciprocity in the relationship between alcohol and depression. This is clearly a murky arena where epidemiologists do battle and pragmatic clinicians might be left wondering on the practical implications of these issues.

The new NICE guidance states that we shouldn't use antidepressants (including SSRIs) routinely for the treatment of alcohol misuse alone. It also suggests that we should treat the alcohol misuse first and if depression or anxiety continues after 3 to 4 weeks of abstinence then assess the depression or anxiety again and consider the appropriate management.

While this seems a reasonable strategy one of the commentaries in Addiction makes a crucial point of which many clinicians will be wary: "*it is essential that clinicians do not take alcohol-induced depression lightly because, like independent depression, it is subjectively painful and confers risk for suicidal behaviour*."

Clinical experience with the treatment of hepatitis C infection in patients on opioid pharmacotherapy. *Sasadeusz JJ, Dore G, Kronborg I, et al. Addiction 2011; 106:977-984*

This paper looks at the efficacy, safety and adherence to hepatitis C therapy in patients attending tertiary hepatitis clinics. A total of 53 patients receiving opioid replacement therapy received pegylated interferon and weight-based ribavirin for either 24 or 48 weeks depending on their hepatitis C virus genotype.

Overall, the sustained virological response (SVR) was 57% and was similar in active injectors and non-injectors. The psychological profile of patients did not change on therapy. The adverse effects were comparable to non-opioid replacement patients.

SMMGP comment: This study showed that active injectors can achieve comparable response rates to other groups with the same number of adverse events and good adherence. This paper

is good news – it is often stated that there should be no barriers to treatment but we still have a poor record for getting active injectors into treatment. However, one could choose to interpret this paper as simple and unsurprising evidence that those with the motivation, determination and gumption to jump through the series of hoops that tertiary care can create are already a carefully selected population. This is the problem here – the treatment was in *tertiary clinics*. For a large number of hepatitis C patients who use substances this is still difficult and we need to see increasing amounts of community treatment. Good secondary care support with good primary care integration remains imperative.

With increasing treatment being undertaken in primary care, the development of the *RCGP Certificate in Detection, Diagnosis and Management of Hepatitis B and C in Primary Care Part 1 and 2* is particularly important. The Part 1 emodule is now available at RCGP e-learning and see SMMGP web site for details of the forthcoming Trainers' Day (in July) and other dates for this Certificate.

Methadone-induced torsades de pointes: A twist of fate. Thanavaro KL, Thanavaro JL. *Heart & Lung. doi:10.1016/j.hrtlng.2010.12.008*

This was a case study of a 61-year old man with a history of smoking, diabetes, hypertension, anaemia, post-traumatic stress disorder and anxiety. He also had a history of previous heroin use and was on 110mg/day methadone.

He presented to the emergency department (ED) after 2 episodes of dizziness and near syncope. When he was seen in the ED he was found to be hypokalaemic, hypomagnesic and his ECG showed he was in normal sinus rhythm with a QTc interval of 626 milliseconds. He was admitted for monitoring and during this period he developed chest pain and palpitations and he went into torsades de pointes (TdP). This was treated with IV magnesium and potassium. His methadone was converted to buprenorphine and 5 months later his ECG was normal except for borderline QTc prolongation at 443 milliseconds.

SMMGP comment: Case reports feature quite low down on the medical evidence hierarchy and are rarely included in this update. However, they still have a role and, in all honesty, they usually have a more compelling narrative than your average meta-analysis. They also offer some scope for the authors to present a potted mini-review of the evidence in keeping with an old-fashioned narrative review which has been superseded by the regimented and rigorous process of the systematic review.

While the overall mortality attributable to methadone and its effect on the QT interval remains contentious most clinicians will have had some experience of its effect on the individual. It is widely accepted that methadone does cause QTc prolongation and therefore puts people at risk of torsades de pointes. It does seem to be dose-dependent and the majority of cases have been in people on more than 100 mg methadone.

One of the key issues is to be particularly wary of other QT prolonging drugs and where there might be a history of prolonged QT syndrome. We also need to consider the impact of other factors such as electrolyte imbalance, renal insufficiency or structural heart disease (as in the case report). It seems clear that we need to continue to raise awareness about the potential for QTc prolongation but we need to maintain pragmatic policies.

The alternative may be inadequate treatment and the risk-benefit is far from clear given the overall improvements in heath status for those on methadone.

Oral naltrexone maintenance treatment for opioid dependence (Review). *Minozzi S, Amato L, Vecchi S et al. Cochrane Database of Systematic Reviews 2011.*

This review set out to evaluate the effects of naltrexone maintenance treatment versus placebo or other treatments in preventing relapse in those with opioid dependence who have been detoxified. They followed the usual thorough process for sifting the evidence base and they ended up with thirteen studies with a total of 1158 participants that met the inclusion criteria. The primary outcomes examined were: abstinence in using heroin measured by participant retention; numbers of participants with negative urinalysis; relapse at follow up; and mortality. Secondary outcomes were side effects and criminal activity.

The results showed that there was no statistically significant difference for any of the primary outcomes. The only statistically significant result was in the secondary outcomes and it showed that naltrexone reduced the risk of incarceration. However, these data came from just two studies and so numbers were overall low and, therefore, potentially unreliable. Retention in studies was around 28% but, overall, it was shown that naltrexone was no better than psychotherapy and it was no better than benzodiazepines or buprenorphine for retention, abstinence and side effects.

SMMGP comment: If there is one thing a Cochrane review is good for it is to remind us just how flimsy the evidence base can be for some interventions. As it stands there is considerably better evidence for naltrexone after alcohol withdrawal than there is for its use after detoxification from opioid dependence. Many of us in clinical practice may offer naltrexone routinely but there is really no clear evidence that naltrexone is superior to other kinds of treatment. This shouldn't necessarily stop us from using it – but the patients that might benefit probably need careful selection given compliance rates have been shown to be so poor.

It is also worth highlighting that none of the studies looked at the issue of deaths from fatal overdoses. This is potentially a highly pertinent area and should remain a key element of the discussion with patients and reminds us of when one state in Australia compared naltrexone and methadone maintenance the study had to be stopped because the death rate was so high in the naltrexone arm.

Treating heavy smokers in primary care with the nicotine nasal spray: randomized placebo-controlled trial *Stapleton JA, Sutherland G. Addiction 2011;106:824-832*

This study sets out to 'broaden the evidence base' by running a trial, based in UK general practice, where only brief support was available for participants while they compared nicotine nasal spray to placebo. It was based in 27 general practices and there was a total of 761 heavy smokers (at least 15 cigs/day for at least 3 years) who received brief support and 12 weeks of treatment with either nicotine nasal spray or placebo. The primary outcome was biochemically-verified complete abstinence from smoking throughout weeks 3-12.

The results showed that nicotine nasal spray more than doubled the number who successfully stopped smoking (15.4% vs 6.7%) from weeks 3-12 giving an odds ratio of 2.6 (95% CI 1.5-4.4). Although many reported minor irritant adverse effects it was noted to be particularly effective amongst those who were 'highly dependent' on nicotine.

SMMGP comment: Tobacco harm reduction strategies is a neglected area although we know

that replacing smoking with a smokeless delivery system for the primary drug, nicotine, can reduce risks by about 99%, about the same as abstinence. Because smoking is so popular, the total health benefits from tobacco harm reduction dwarf those from any other area of HR.

There is an increasing array of nicotine replacement therapy options and this study shows one effective way of delivery. One interesting facet was the tiny number (0.2%) that went on to achieve abstinence if they were still smoking at one week. This infers that it may be worth prescribing a single week of nicotine nasal spray and reassessing abstinence. It's a relatively small, inexpensive punt and it can double the chance of abstinence for that individual – even without the more comprehensive smoking cessation services which some prescribing is based around.

Oral health of substance-dependent individuals: Impact of specific substances *D'Amore MM, Cheng DM, Kressin NR, et al. Journal Substance Abuse Treatment 2011. Epub ahead of print.*

This study looked at the respective effects of alcohol, stimulants, opioids and marijuana on oral health in substance-dependent persons. They used self-reported data from 563 individuals.

Most reported unsatisfactory oral health and their most recent dental visit was more than 1 year ago. When subjected to multivariable logistic regression analysis none of the substances were significantly associated with oral health status. However, an adjusted analysis did show a worse overall oral health rating compared to 1 year ago associated with opioid use. The basic data in the sample showed that 29% of the sample had six or more teeth removed and this compares with the general population where we would expect it to be around 8.5%.

SMMGP comment: It has been a stubborn myth that methadone can rot teeth but few would dispute the alarmingly poor dentition in those with opioid dependence. Factors such as limited access to dental care, poor nutrition, and poor oral hygiene all play a part. This paper highlights that the oral health of alcohol, stimulant and even cannabis users is little better.

There isn't much doubt about the associations of poor oral health – tooth loss, cerebrovascular disease and pulmonary infection amongst others. It may be that oral health is the most obvious manifestation of poor physical health – the mouth being a window, as it were, to allow us to peer into an individual's health status. However, it is also worth bearing in mind that the causal pathway may also flow in the other direction – poor oral health contributing to problems such as cardiovascular disease. We should be regarding oral health problems as a co-morbidity with substance use and good access to dental care should be hardwired into the management of all those with substance misuse issues. And always remember that dental pain is one of the top reasons for relapse on to drugs.

A web-based survey on mephedrone. *Carhart-Harris RL, King LA, Nutt DJ. Drug and Alcohol Dependence 2011. Epub ahead of print.*

This survey was conducted between May and September 2010 just after the UK ban on mephedrone in April 2010. The survey consisted of 56 questions and took around 20-30 minutes to complete. Participants should have taken mephedrone on at least one occasion in the past.

A total of 1506 forms were received. The modal number of lifetime uses was 11-50 and 80% first used mephedrone in 2010 or 2009. The modal amount taken in a session was 'about 500mg'. The most popular route of administration was intranasal with 57% and 28% took it orally.

Mephedrone was compared more closely to MDMA than cocaine and 73% of those who had taken MDMA said they preferred mephedrone.

Around 1 in 5 had experienced a 'significant negative reaction' and these were typically anxiety, panic and palpitations. A little over 1 in 5 had experienced skin discolouration (e.g. blotches on chest or blue/purple fingers or joints) as an adverse effect.

Around half said they found mephedrone addictive and the results also strongly suggested that the majority of respondents would use it less given it has now been made illegal.

SMMGP comment: Clearly there are limitations with web surveys and there is no way to verify the accuracy of the information against controls. Most of the traffic to the survey came via other drug user websites and it is probable this biased the sample towards experienced drug users.

Most people would agree that there is something of a paucity of data on these newer drugs and their effects. There are a large number of responses in this survey and this helps to shed light on the issue. It is also clear that we are going to be forever playing catch up with these drugs. Most mephedrone users came to it in just the year before it was made illegal and the survey suggests that most will return to using MDMA now. Presumably many will turn to the next legal high - of which we have even less information.

A good resource for more information on legal highs and novel substances is the Recreational Drugs European Network (ReDNet) launched at the School of Pharmacy, University of Hertfordshire in April 2010 with the objective of constituting one of the first ICT prevention programmes designed for novel psychoactive compounds in the field of eHealth prevention across Europe. See article in Network 32 and/or **http://tinyurl.com/Recreate-Drugs**